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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/852,020	05/06/97	MARUYAMA I	RD

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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1636	R0

DATE MAILED: 07/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/852,020	Maruyama, et al
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

☒ Responsive to communication(s) filed on *Apr 21, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *57-60* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *57-60* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment filed 4/21/00.**

Claims 57-60 encompass recombinant lambdoid bacteriophage vectors or bacteriophage having a cistron comprising the coding sequence for an anchor matrix gene operatively linked to coding sequences for a linker polypeptide and a desired, preselected polypeptide such that expression of the recombinant cistron during morphogenesis results in incorporation and display of the recombinant fusion polypeptide comprising the desired polypeptide sequence on the surface of the mature lambdoid phage particle. The claims encompass any of the potential anchor matrix polypeptides (e.g. head proteins: pE, pD, pB, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM and pT; page 22 lines 13-21), or portions thereof, as the matrix anchor

component of the fusion polypeptide which is displayed on the surface of the phage particle. Each of these polypeptides has its own unique structure and plays a unique role in phage morphogenesis, having a distinct set of temporal and spatial interactions with other phage proteins during the assembly of the mature phage particle. Thus, the instant claims are very broad genus claims directed to a number of distinct structural polypeptides having different structural and functional characteristics.

While the specification has described adequately one subset of the claimed genus, those embodiments drawn to the tail polypeptide pV, there is only the broadest description of any of the remaining members of the genus. The claims and specification only describe a conditionally expressible cistron encoding an anchor matrix polypeptide operatively linked to a linker polypeptide coding sequence which is in turn linked to the coding sequence for a desired, preselected polypeptide. There is no description of where within the coding sequence for any of the other members of the genus of potential anchor matrix polypeptides one would insert the sequences for the linker polypeptide and the desired polypeptide. There is no description within the prior art or within the specification as to which portions of any of the other anchor matrix polypeptides might be dispensable for morphogenesis and thus potentially suitable for insertion of foreign sequences. There are no relevant examples in the specification of such a fusion construct for any of the potential anchor matrix polypeptides other than pV. Because of the unique sequences, structural features and functions for each of the other anchor matrix proteins, one of skill in the art can not extrapolate from the descriptions of fusion constructs comprising

pV what would be a permissible insertion and fusion for any of the other anchor matrix proteins such that a recombinant polypeptide expressed from such a construct would be assembled and displayed on the surface of the mature phage particle. Thus, it would not be possible for the skilled artisan to envision a representative number of the remaining members of the claimed genus of recombinant anchor-matrix fusions. Therefore, there is not sufficient description in the specification to inform a skilled artisan that the applicant was in possession of the full, large breadth of the claimed invention, a recombinant lambdoid bacteriophage vector or bacteriophage comprising a cistron encoding an anchor matrix polypeptide other than pV operatively linked to the coding sequences for a linker polypeptide and desired, preselected polypeptide for display of the recombinant fusion protein on the surface of the mature phage particle.

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant lambdoid bacteriophage vector or bacteriophage comprising fusions with lambdoid bacteriophage tail polypeptides that are pV, does not reasonable provide enablement for embodiments wherein the lambdoid phage anchor matrix protein is other than pV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. **This is a new rejection necessitated by applicants' amendment filed 4/21/00.** These claims were rejected previously (as claims 30, 35, 40 and 45) under 35 U.S.C. 112, first paragraph, in the Office Action filed 8/3/98 (Paper No. 10). Similar claims (claims 1,

2, 11 and 15) drawn towards a recombinant lambdoid bacteriophage vector or bacteriophage comprising fusions with a lambdoid tail protein, and thus slightly less broad in scope than the instant claims, were rejected under 35 U.S.C. 112, first paragraph, in the Office Action filed 12/23/97 (Paper No. 7).

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the art, state of the prior art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The nature of the invention is complex, involving a recombinant lambdoid bacteriophage which displays on the surface of the bacteriophage a fusion protein including one of the anchor matrix proteins operatively linked in the direction of the amino terminus to the carboxy terminus to a linker polypeptide and a polypeptide of choice. This invention involves complex issues of which phage matrix polypeptides are suitable for forming such fusion proteins both in terms of accessible display on the outer surface of the phage and the ability of the phage to assemble properly once the fusion protein is expressed during morphogenesis. Once a suitable matrix polypeptide has been identified, there are still complex issues as to where to insert the linker and preselected polypeptide into the desired matrix polypeptide such that assembly is not impaired and accessible display is maintained. Issues of what size and type of polypeptide will be tolerated and displayed in an accessible manner for each desired polypeptide are also present for

the instant claims. The breadth of the claims, encompassing any of the proteins displayed on the surface of the phage particle (e.g. head proteins: pE, pD, pB, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM and pT; page 22 lines 13-21), greatly increases the complexity of the invention with regard to how each potential matrix anchor protein is assembled into the phage, the role each potential matrix anchor protein plays in morphogenesis and assembly (i.e. is it dispensable for assembly or function?) and where within the coding region for the potential matrix anchor protein to insert the coding sequences for the polypeptide linker and preselected polypeptide in order to express a fusion protein that will allow its incorporation into the phage capsid in such a way as to allow morphogenesis to proceed and accessible display of the preselected protein on the mature phage particle.

The specification provides specific guidance and working examples only for the major tail protein pV and the prior art is silent on fusion proteins that include the other tail proteins or head proteins of lambdoid phage. Reference to the other outer-surface proteins of the phage particle is only suggestive that they are suitable for use in the invention by virtue of their location on the surface of the phage tail or capsid. There is no guidance within the specification or the prior art regarding which portions of the other potential matrix anchor proteins are dispensable for assembly and which may present suitable locations for insertion of heterologous sequences. There is no guidance within the specification or prior art as to which particular nucleotide sequence within the gene encoding any potential matrix anchor protein, other than pV, is suitable for insertion of a heterologous coding sequence such that the expressed fusion protein from such

a construct will not disrupt particle assembly and will allow functional, accessible display of the desired, preselected polypeptide on the mature phage particle.

The art of displaying a desired polypeptide in an accessible manner on a phage particle is not predictable, as evidence by applicants' own teachings. The specification discloses that the pV is present in 180-200 copies in the mature tail. The specification teaches (page 115, 1st paragraph) that addition of a linker polypeptide appears to interfere with tail assembly, since the plaques were smaller in su^+ hosts. Further, at page 126 of the specification it is disclosed that phage tails displaying beta-galactosidase contained only one to a few copies of the fusion polypeptide even though higher levels of incorporation could have been expected, indicating that the fusion polypeptide interfered with some aspect of tail assembly. These findings illustrate that even though the carboxy terminus of pV is dispensable, fusion to a foreign polypeptide interferes with some aspect of tail assembly or infection. Therefore, successful incorporation into a mature tail of pV protein fusions is somewhat unpredictable.

Each of the matrix proteins occupies a unique position in the mature particle, and performs a unique role during particle assembly. The successful incorporation into the tail of altered forms of one of the tail proteins (e.g. pV) does not provide evidence that any of the other matrix proteins (head or tail polypeptides) can be similarly modified without impairing their unique role in phage assembly. With respect to the pV protein, it was known in the prior art that this protein comprised a "knob" that extended out from the surface of the phage that was dispensable. It is this "knob" that is replaced by the displayed peptide in the disclosed invention.

Replacement of this knob with heterologous peptide sequence would not have been expected *a priori* to interfere with phage assembly, however, as disclosed in the instant specification it was necessary to replace the knob with the desired peptide in only a limited number of recombinant pV subunits in the phage tail, or assembly was impaired. It is for this reason that Ladner is not deemed to be prior art for the prophetic disclosure of using pV peptide fusions to display proteins. No comparable dispensable peptide sequence is disclosed in either the specification or the prior art that one could have expected could be replaced with a desired peptide, without interfering with phage assembly. As recited in the claims, the fusion polypeptide comprises, from amino to carboxy terminus, a matrix anchor polypeptide, a linker polypeptide and a preselected polypeptide. Such an arrangement would therefore require that the carboxy terminus of a given matrix anchor protein be exposed on the surface of the particle and that addition of other polypeptides to the carboxy terminus of the matrix anchor polypeptide not interfere with either expression of the matrix anchor gene or assembly of the matrix anchor/preselected polypeptide fusion into the phage.

Applicants have submitted Mikawa et al (Exhibit I; Paper No. 8) as evidence of enablement for other capsid or tail proteins. However, Mikawa et al is not prior art and it is not clear that the methods used to obtain phage displaying polypeptides as pD fusions are commensurate with the teachings in the instant disclosure. For example, amino terminal fusions were made between the second and third codons, rather than at or after the initial codon (page 22, column 1). It is also noted that the primary author, Y.G. Mikawa, is not a named inventor on the

instant application, which suggests that the contribution of Y.G. Mikawa is in addition to the instant disclosure. With regard to the predictability of making fusions comprising pD as the matrix anchor portion of the fusion polypeptide, it is of note that the reference states in the first paragraph of the discussion (page 27) that the ends of pD are not involved in the interaction between pD subunits or between pD and pE subunits, "an important result for which no guarantee existed at the start of this work.". As indicated above, there is no teaching or working example in the instant specification that indicates where in the pD coding sequence (or in the coding sequence of any of the other potential matrix anchor proteins) it is appropriate to insert coding sequences for the linker polypeptide and the preselected protein such that interaction among capsid components is not interrupted, that phage assembly is not impaired and the desired fusion protein is displayed in a functional, accessible manner. Also, as with pV, one cannot extrapolate from pD fusions where to make fusions to other capsid proteins, such that phage assembly is not impaired. Mikawa et al specifically states that the authors chose pD because it was dispensable provided the genome was less than 82% of wild type in length, a feature not true for the other capsid proteins.

Given the complex nature of the invention in which a fusion polypeptide comprising an anchor motif from the bacteriophage matrix is expressed during phage morphogenesis such that the fusion polypeptide is incorporated into the phage structure and displayed in an accessible and/or functional manner, the breadth of the claims which encompass any of the potential matrix anchor polypeptides displayed on the surface of the phage particle, the lack of guidance from the

specification or the prior art as to which portions of any of the other potential matrix anchor proteins are dispensable for phage assembly or which would be appropriate for insertion of the coding sequences for the polypeptide linker and preselected polypeptide (even for pD) and the unpredictability of whether a particular fusion will be incorporated into the phage particle in a fashion that does not disrupt subunit-subunit interaction and will allow accessible and/or functional display of the desired, preselected polypeptide on the mature particle, it would require undue, unpredictable experimentation to make even one embodiment of the claimed invention not involving pV as the matrix anchor protein. One would first have to first envision an appropriate matrix anchor protein construct in which the coding sequence for the matrix anchor protein is operatively linked at a particular sequence with the coding sequences for a linker polypeptide and desired, preselected polypeptide, make the construct and express the hybrid gene during morphogenesis such that the fusion protein might be incorporated into the phage particle and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner. If unsuccessful, which is likely given the lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle assembly and the unpredictability of the art as evidence by applicants' own teachings regarding pV, it would then be necessary for one of skill in the art to envision a modification of the first matrix anchor/fusion protein construct, or an entirely different construct, which might be suitable for display of a desired, preselected protein on the surface of the phage particle, make the construct

and express the hybrid gene during morphogenesis such that the second fusion protein might be incorporated into the phage particle and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner. If again unsuccessful, which is likely given the lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle assembly and the unpredictability of the art as evidence by applicants' own teachings regarding pV, it would be necessary for one of skill in the art to repeat the entire process until such time, if any, that a construct was identified which allows the expression of a fusion protein comprising one of the potential matrix anchor proteins with a desired, preselected polypeptide such that the fusion protein is successfully incorporated into the mature phage particle and the preselected polypeptide displayed in an accessible and/or functional manner. Such experimentation is undue, unpredictable experimentation and would be required in order to make and use any embodiment of the instant invention not comprising pV as the matrix anchor portion of the fusion protein, even the pD fusions of Mikawa et al, in light of the instant specification. Thus, applicants' claimed invention of a recombinant lambdoid bacteriophage vector or bacteriophage encoding protein fusions derived from any matrix anchor protein located on the surface of the phage particle operatively linked to a polypeptide linker and preselected polypeptide, is not considered to be fully enabled by the specification. Only in the case where the matrix anchor protein is derived from the pV polypeptide, as described in the specification, would there be a reasonable expectation of success in constructing a vector or bacteriophage

which encodes a fusion polypeptide comprising the desired, preselected polypeptide expressed in an accessible and/or functional manner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57-58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 5,627,024. **This is a new rejection necessitated by applicants' amendment filed 4/21/00.** Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reason.

Claims 1-2 of '024 are drawn to a recombinant lambdoid bacteriophage vector comprising a conditionally suppressible cistron for the conditional expression of a tail protein or a fusion

protein which itself comprises a first upstream translatable sequence that encodes a pV lambdoid bacteriophage tail protein operatively linked to additional sequences. Claims 57-58 of the instant application are drawn to a recombinant lambdoid bacteriophage vector comprising a conditionally suppressible cistron for the conditional expression of a matrix anchor protein or a fusion protein which itself comprises a first upstream translatable sequence that encodes a lambdoid bacteriophage matrix anchor protein (e.g. pV, pM, pD, pJ, pG and pT) operatively linked to additional sequences. Thus, the instant claims are broader in scope and totally encompass claims 1-2 of the '024 patent. The instant claims, if allowed, would extend patent protection of the recombinant lambdoid bacteriophage vectors of the '024 patent, in addition to providing patent protection to the recombinant vectors of the instant invention not encompassed by the '024 patent (i.e. wherein the matrix anchor protein is other than pV). Also, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the '024 patent, then two different assignees would hold a patent toe the claimed bacteriophage vector of '024, and thus improperly, there would be possible harassment by multiple assignees.

Claims 59-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-10 of U.S. Patent No. 5,627,024. **This is a new rejection necessitated by applicants' amendment filed 4/21/00.** Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant

claims embrace the claimed invention of the '024 patent. Claims 9-10 of the '024 patent are drawn to a recombinant bacteriophage comprising a fusion protein wherein the fusion protein comprises, in the direction of amino terminus to carboxy terminus, a pV lambdoid bacteriophage tail polypeptide, a linker polypeptide and a preselected polypeptide. Claims 59-60 of the instant application is drawn to a recombinant bacteriophage comprising a fusion protein wherein the fusion protein consists of, in direction of amino terminus to carboxy terminus, a bacteriophage matrix anchor protein (e.g. pV, pM, pJ, pG, pD or pT), a linker polypeptide and a preselected polypeptide. Thus the present invention is an obvious variant of the recombinant bacteriophage of the '024 patent in that the present invention merely substitutes another matrix anchor protein other than pV as part of the fusion polypeptide displayed on the surface of the phage specified in claims 9-10 of the '024 patent. The instant claims, if allowed, would extend patent protection of the recombinant phage of the '024 patent which possesses a fusion protein consisting of pV operatively linked to a linker polypeptide and a preselected polypeptide, in addition to providing patent protection to the recombinant phage of the instant claims not encompassed by claims 9-10 of the '024 patent (i.e. phage wherein the matrix anchor portion of the fusion protein is a matrix anchor protein other than pV). Also, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the '024 patent, then two different assignees would hold a patent to the claimed bacteriophage of the '024 patent. Thus, improperly, there would be possible harassment by multiple assignees.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "pV" in step (e) of the claim.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00AM to about 5:30PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GLJr

G. Leffers, Jr.
Patent Examiner
Art Unit 1636

June 30, 2000

TERRY MCKELVEY
PRIMARY EXAMINER